PIPECOLIC ACID DERIVATIVE HAIR GROWTH COMPOSITIONS AND USES

This application is a continuation-in-part of U.S. Patent Application No. 08/869,426, filed on June 4, 1997, the entire contents of which are herein incorporated by reference.

BACKGROUND OF THE INVENTION

1. Field of Invention

This invention relates to pharmaceutical compositions and methods for treating alopecia and promoting hair growth using pipecolic acid derivatives.

2. Description of Related Art

Hair loss occurs in a variety of situations. These situations include male pattern alopecia, alopecia senilis, alopecia areata, diseases accompanied by basic skin lesions or tumors, and systematic disorders such as nutritional disorders and internal secretion disorders. The mechanisms causing hair loss are very complicated, but in some instances can be attributed to aging, genetic disposition, the activation of male hormones, the loss of blood supply to hair follicles, and scalp abnormalities.

The immunosuppressant drugs FK506, rapamycin and cyclosporin are well known as potent T-cell specific

immunosuppressants, and are effective against graft rejection after organ transplantation. It has been reported that topical, but not oral, application of FK506 (Yamamoto et al., J. Invest. Dermatol., 1994, 102, 160-164; Jiang et al., J. Invest. Dermatol. 1995, 104, 523-525) and cyclosporin (Iwabuchi et al., J. Dermatol. Sci. 1995, 9, 64-69) stimulates hair growth in a dose-dependent manner. One form of hair loss, alopecia areata, is known to be associated with autoimmune activities; hence, topically administered immunomodulatory compounds are expected to demonstrate efficacy for treating that type of hair loss. The hair growth stimulating effects of FK506 have been the subject of an international patent filing covering FK506 and structures related thereto for hair growth stimulation (Honbo et al., EP 0 423 714 A2). Honbo et al. discloses the use of relatively large tricyclic compounds, known for their immunosuppressive effects, as hair revitalizing agents.

The hair growth and revitalization effects of FK506 and related agents are disclosed in many U.S. patents (Goulet et al., U.S. Patent No. 5,258,389; Luly et al., U.S. Patent No. 5,457,111; Goulet et al., U.S. Patent No. 5,532,248; Goulet et al., U.S. Patent No. 5,189,042; and Ok et al., U.S. Patent No. 5,208,241; Rupprecht et al., U.S. Patent No. 5,284,840; Organ et al., U.S. Patent No. 5,284,877). These patents claim FK506 related compounds. Although

they do not claim methods of hair revitalization, they disclose the known use of FK506 for effecting hair growth. Similar to FK506 (and the claimed variations in the Honbo et al. patent), the compounds claimed in these patents are relatively large. Further, the cited patents relate to immunomodulatory compounds for use in autoimmune related diseases, for which FK506's efficacy is well known.

Other U.S. patents disclose the use of cyclosporin and related compounds for hair revitalization (Hauer et al., U.S. Patent No. 5,342,625; Eberle, U.S. Patent No. 5,284,826; Hewitt et al., U.S. Patent No. 4,996,193). These patents also relate to compounds useful for treating autoimmune diseases and cite the known use of cyclosporin and related immunosuppressive compounds for hair growth.

However, immunosuppressive compounds by definition suppress the immune system and also exhibit other toxic side effects. Accordingly, there is a need for non-immunosuppressant, small molecule compounds which are useful as hair revitalizing compounds.

Hamilton and Steiner disclose in U.S. Patent No. 5,614,547 novel pyrrolidine carboxylate compounds which bind to the immunophilin FKBP12 and stimulate nerve growth, but which lack immunosuppressive effects. Unexpectedly, it has been discovered that

these non-immunosuppressant compounds promote hair growth with an efficacy similar to FK506. Yet their novel small molecule structure and non-immunosuppressive properties differentiate them from FK506 and related immunosuppressive compounds found in the prior art.

SUMMARY OF THE INVENTION

The present invention relates to a method for treating alopecia or promoting hair growth in an animal, which comprises administering to said animal an effective amount of a pipecolic acid derivative.

The present invention further relates to a pharmaceutical composition which comprises:

(i) an effective amount of a pipecolic acid derivative for treating alopecia or promoting hair growth in an animal; and

(ii) a pharmaceutically acceptable carrier.

The pipecolic acid derivatives used in the inventive methods and pharmaceutical compositions include immunosuppressive and non-immunosuppressive compounds having an affinity for FKBP-type immunophilins, particularly FKBP12. Non-immunosuppressive compounds, as their name suggests, do not exert any significant immunosuppressive activity.

BRIEF DESCRIPTION OF THE DRAWINGS

FIG. 1 is a photograph of mice treated with a vehicle after six weeks. FIG. 1 shows that less than 3% of the shaved area is covered with new hair growth when the vehicle (control) is administered.

FIG. 2 is a photograph of mice treated with 10 μM of a pipecolic acid derivative, GPI 1116, after six weeks. FIG. 2 shows that 90% of the shaved area is covered with new hair growth when GPI 1116 is administered.

FIG. 3 is a photograph of mice treated with 3 μM of a pipecolic acid derivative, GPI 1102, after six weeks. FIG. 3 shows that 90% of the shaved area is covered with new hair growth when GPI 1102 is administered.

FIG. 4 is a bar graph plotting the hair growth scores of unshaven animals and shaven animals treated with a vehicle, GPI 1116 (1 μM and 10 μM), GPI 1102 (1 μM and 3 μM), and a related pipecolic acid derivative neuroimmunophilin FKBP ligand, GPI 1044 (1 μM, 3 μM and 10 μM).

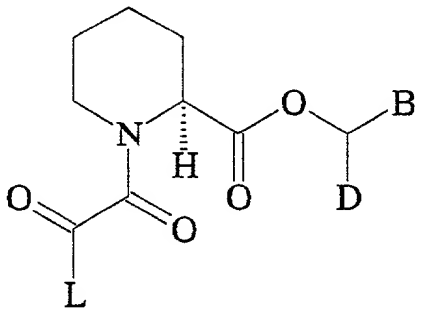
FIG. 5 is a bar graph depicting the relative hair growth indices for C57 Black 6 mice treated with a vehicle, FK506, related neuroimmunophilin FKBP ligand GPI 1206, and GPI 1116, 14 days after treatment with each identified compound. Figure 5 demonstrates the remarkable early hair growth promoted by neuro-immunophilin FKBP ligands.

DETAILED DESCRIPTION OF THE INVENTION

Definitions

"Alopecia" refers to deficient hair growth and partial or complete loss of hair, including without limitation androgenic alopecia (male pattern baldness), toxic alopecia, alopecia senilis, alopecia areata, alopecia pelada and trichotillomania. Alopecia results when the pilar cycle is disturbed. The most frequent phenomenon is a shortening of the hair growth or anagen phase due to cessation of cell proliferation. This results in an early onset of the catagen phase, and consequently a large number of hairs in the telogen phase during which the follicles are detached from the dermal papillae, and the hairs fall out. Alopecia has a number of etiologies, including genetic factors, aging, local and systemic diseases, febrile conditions, mental stresses, hormonal problems, and secondary effects of drugs.

"GPI 1044" refers to a compound of formula



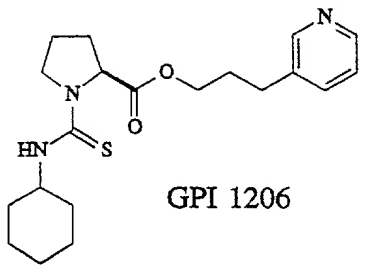
wherein B is 3-Phenylpropyl, D is 3-Phenylpropyl, and L is Phenyl.

"GPI 1102" refers to Compound 98, 4-phenyl-1-(3-phenylpropyl)butyl 1-(3,3-dimethyl-2-oxopentanoyl)-2-

piperidinecarboxylate.

"GPI 1116" refers to Compound 103, 1-phenethyl-3-phenylpropyl 1-(3,3-dimethyl-2-oxopentanoyl)-2-piperidinecarboxylate.

"GPI 1206" refers to a compound of formula



GPI 1206

"Isomers" refer to different compounds that have the same molecular formula. "Stereoisomers" are isomers that differ only in the way the atoms are arranged in space. "Enantiomers" are a pair of stereoisomers that are non-superimposable mirror images of each other. "Diastereoisomers" are stereoisomers which are not mirror images of each other. "Racemic mixture" means a mixture containing equal parts of individual enantiomers. "Non-racemic mixture" is a mixture containing unequal parts of individual enantiomers or stereoisomers.

"Pharmaceutically acceptable salt, ester, or solvate" refers to a salt, ester, or solvate of a subject compound which possesses the desired pharmacological activity and which is neither biologically nor otherwise undesirable. A salt, ester, or solvate can be formed with inorganic acids

such as acetate, adipate, alginate, aspartate, benzoate, benzenesulfonate, bisulfate, butyrate, citrate, camphorate, camphorsulfonate, cyclopentanepropionate, digluconate, dodecylsulfate, ethanesulfonate, fumarate, glucoheptanoate, gluconate, glycerophosphate, hemisulfate, heptanoate, hexanoate, hydrochloride, hydrobromide, hydroiodide, 2-hydroxyethanesulfonate, lactate, maleate, methanesulfonate, naphthylate, 2-naphthalenesulfonate, nicotinate, oxalate, sulfate, thiocyanate, tosylate and undecanoate. Eamples of base salts, esters, or solvates include ammonium salts; alkali metal salts, such as sodium and potassium salts; alkaline earth metal salts, such as calcium and magnesium salts; salts with organic bases, such as dicyclohexylamine salts; N-methyl-D-glucamine; and salts with amino acids, such as arginine, lysine, and so forth. Also, the basic nitrogen-containing groups can be quarternized with such agents as lower alkyl halides, such as methyl, ethyl, propyl, and butyl chlorides, bromides, and iodides; dialkyl sulfates, such as dimethyl, diethyl, dibutyl, and diamyl sulfates; long chain halides, such as decyl, lauryl, myristyl, and stearyl chlorides, bromides, and iodides; aralkyl halides, such as benzyl and phenethyl bromides; and others. Water or oil-soluble or dispersible products are thereby obtained.

"Pilar cycle" refers to the life cycle of hair follicles, and includes three phases:

(1) the anagen phase, the period of active hair growth which, insofar as scalp hair is concerned, lasts about three to five years;

(2) the catagen phase, the period when growth stops and the follicle atrophies which, insofar as scalp hair is concerned, lasts about one to two weeks; and

(3) the telogen phase, the rest period when hair progressively separates and finally falls out which, insofar as scalp hair is concerned, lasts about three to four months.

Normally 80 to 90 percent of the follicles are in the anagen phase, less than 1 percent being in the catagen phase, and the rest being in the telogen phase. In the telogen phase, hair is uniform in diameter with a slightly bulbous, non-pigmented root. By contrast, in the anagen phase, hair has a large colored bulb at its root.

"Promoting hair growth" refers to maintaining, inducing, stimulating, accelerating, or revitalizing the germination of hair.

"Treating alopecia" refers to:

(i) preventing alopecia in an animal which may be predisposed to alopecia; and/or

(ii) inhibiting, retarding or reducing alopecia; and/or

(iii) promoting hair growth; and/or

(iv) prolonging the anagen phase of the hair cycle; and/or

(v) converting vellus hair to growth as terminal hair. Terminal hair is coarse, pigmented, long hair in which the bulb of the hair follicle is seated deep in the dermis. Vellus hair, on the other hand, is fine, thin, non-pigmented short hair in which the hair bulb is located superficially in the dermis. As alopecia progresses, the hairs change from the terminal to the vellus type.

Methods of the Present Invention

The present invention relates to a method for treating alopecia or promoting hair growth in an animal, which comprises administering to said animal an effective amount of a pipecolic acid derivative.

The inventive method is particularly useful for treating male pattern alopecia, alopecia senilis, alopecia areata, alopecia resulting from skin lesions or tumors, alopecia resulting from cancer therapy such as chemotherapy and radiation, and alopecia resulting from systematic disorders such as nutritional disorders and internal secretion disorders.

Pharmaceutical Compositions of the Present Invention

The present invention also relates to a pharmaceutical composition comprising:

(i) an effective amount of a pipecolic acid derivative for treating alopecia or promoting hair growth in an animal; and

(ii) a pharmaceutically acceptable carrier.

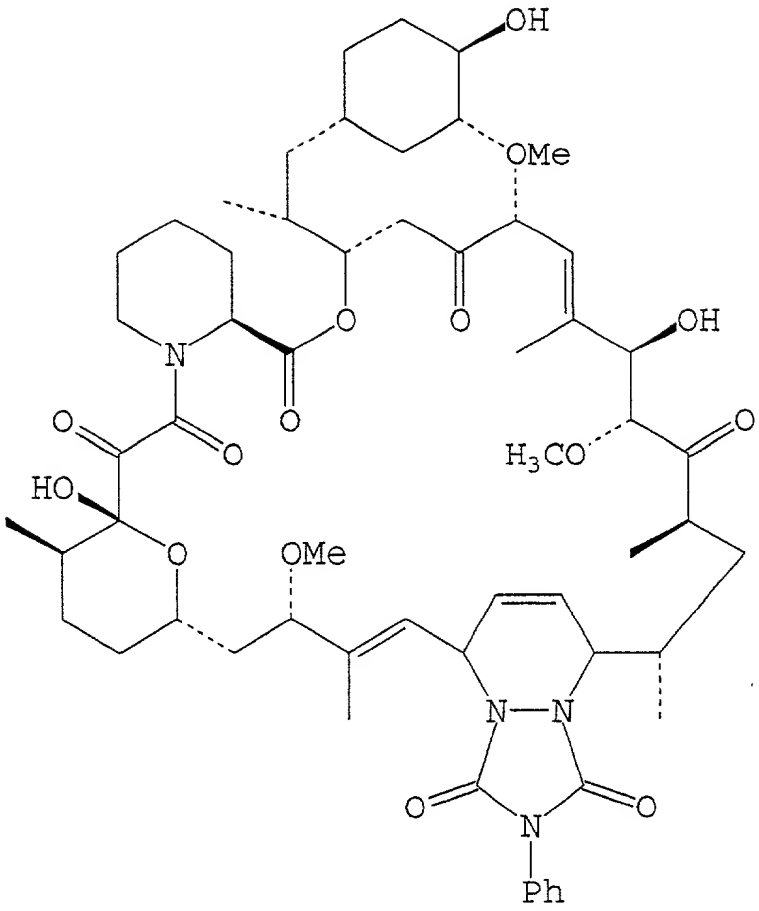
PIPECOLIC ACID DERIVATIVES

The pipecolic acid derivatives used in the methods and pharmaceutical compositions of the present invention have an affinity for FKBP-type immunophilins, such as FKBP12. When a pipecolic acid derivative binds to an FKBP-type immunophilin, it has been found to inhibit the prolyl-peptidyl *cis-trans* isomerase, or rotamase, activity of the binding protein. Unexpectedly, the compounds have also been found to stimulate hair growth. These rotamase inhibiting compounds may be immunosuppressive or non-immunosuppressive. Examples of useful compounds are set forth below.

COMPOUND 1

Ocain et al., *Biochemical and Biophysical Research Communications*, Vol. 192, No. 3, 1993, incorporated herein by reference, discloses an exemplary pipecolic acid derivative represented by Formula I. The compound was synthesized at Wyeth-Ayerst by Dr. Phil Hughes by reaction of 4-phenyl-1,2,4-triazoline-3,5-dione with rapamycin.

FORMULA I



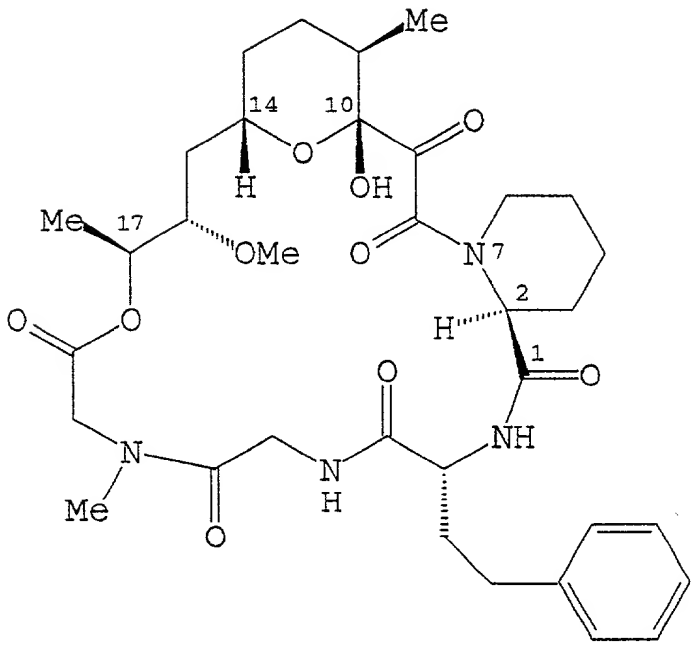
I

Way-124,466

COMPOUND 2

Chakraborty et al , *Chemistry and Biology*, Vol. 2, pp. 157-161, March 1995, incorporated herein by reference, discloses an exemplary pipecolic acid derivative represented by Formula II.

FORMULA II



II

RAP-Pa

COMPOUNDS 3-5

Ikeda et al., *J. Am. Chem. Soc.*, Vol. 116, pp. 4143-4144, 1994, incorporated herein by reference, discloses exemplary pipecolic acid derivatives represented by Formula III and Table I.

FORMULA III

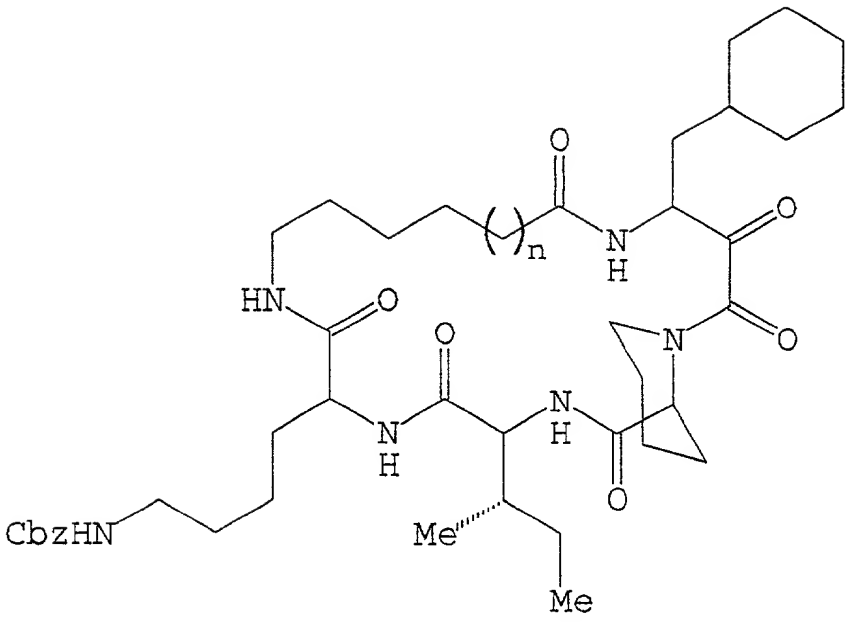


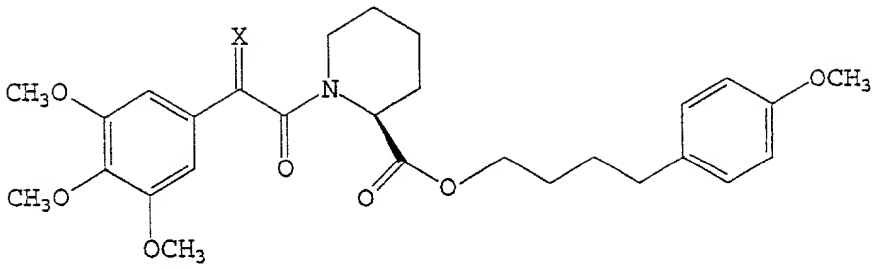
TABLE I

Compound	Structure
3	n = 1
4	n = 2
5	n = 3

COMPOUNDS 6-9

Wang et al., *Bioorganic and Medicinal Chemistry Letters*, Vol. 4, No. 9, pp. 1161-1166, 1994, incorporated herein by reference, discloses exemplary pipecolic acid derivatives represented by Formula IV and Table II.

FORMULA IV



IV

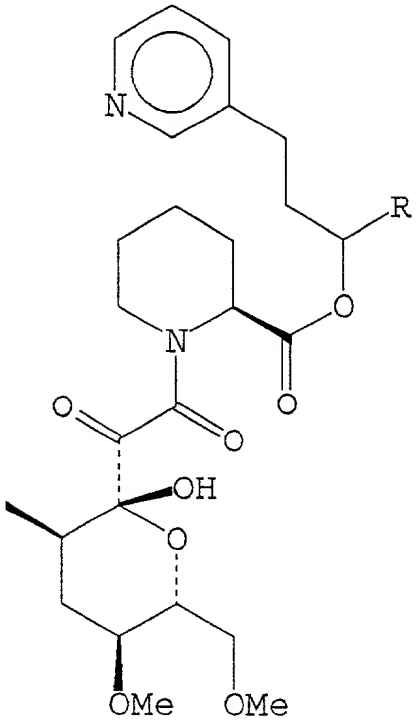
TABLE II

Compound	Structure
6	X = H, H
7	X = CH_2
8	X = H, CH_3
9	X = O

COMPOUND 10

Birkenshaw et al., *Bioorganic & Medicinal Chemistry Letters*, Vol. 4, No. 21, pp. 2501-2506, 1994, incorporated herein by reference, discloses an exemplary pipecolic acid derivative represented by Formula V.

FORMULA V

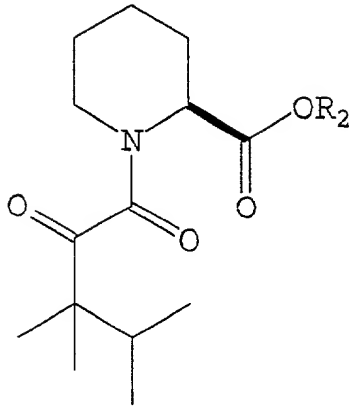


V

COMPOUNDS 11-21

Holt et al., *J. Am. Chem. Soc.*, Vol. 115, pp. 9925-9938, 1993, incorporated herein by reference, discloses exemplary pipecolic acid derivatives represented by Formula VI and Tables III and IV.

FORMULA VI



VI

TABLE III

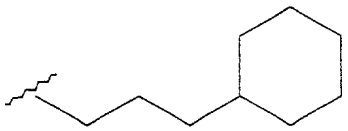
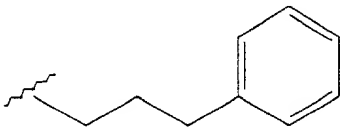
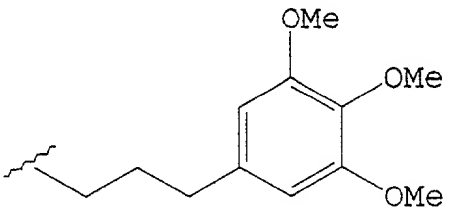
Compound	R_2
11	
12	
13	

TABLE III (continued)

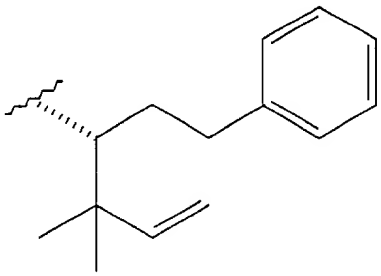
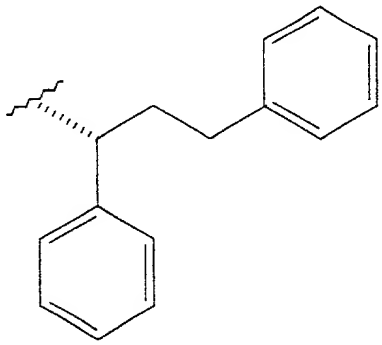
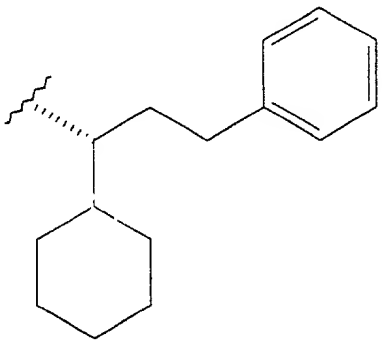
Compound	R_2
14	
15	
16	

TABLE III (continued)

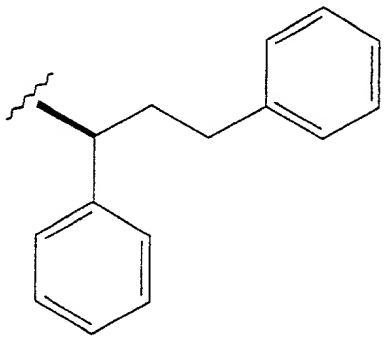
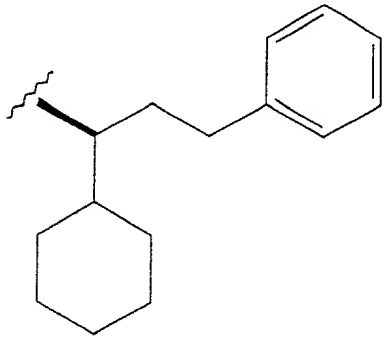
Compound	R_2
17	
18	

TABLE IV

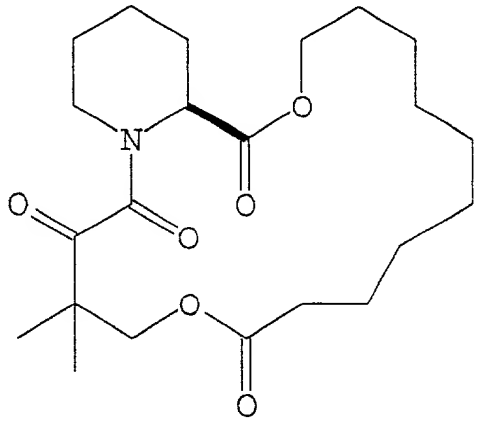
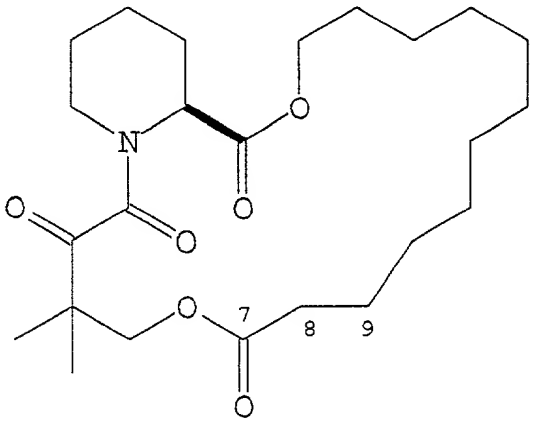
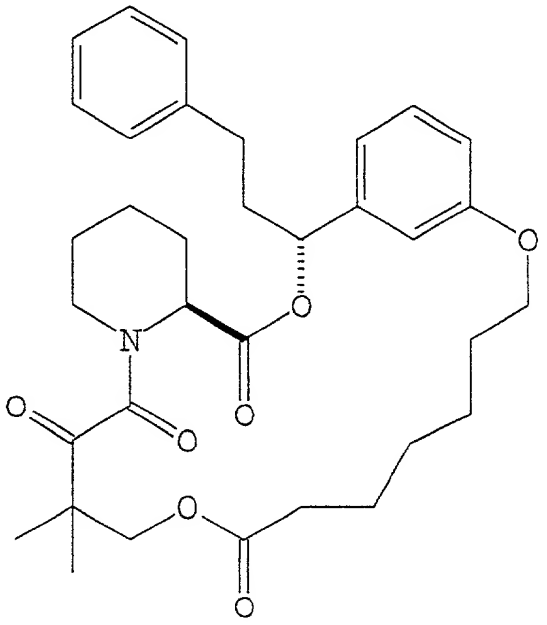
Compound	Structure
19	
20	

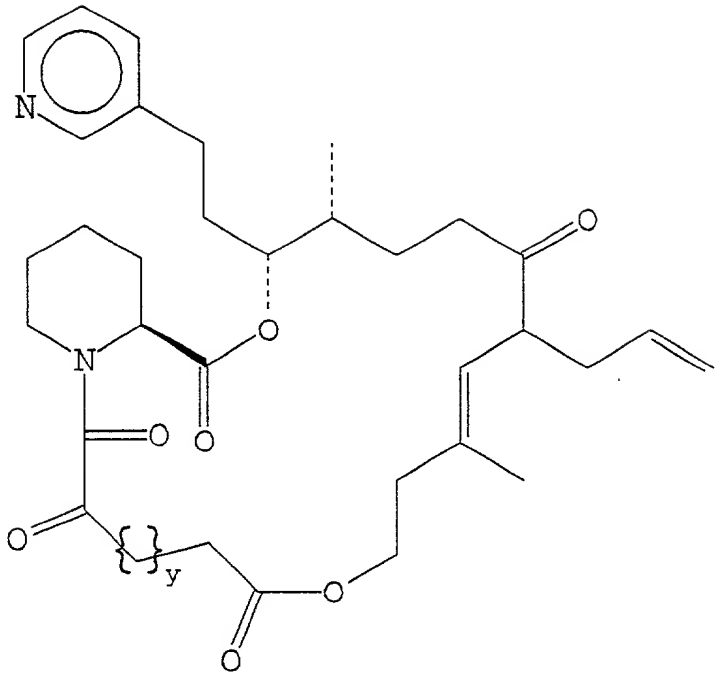
TABLE IV (continued)

Compound	Structure
21	

COMPOUNDS 22-30

Caffery et al., *Bioorganic & Medicinal Chemistry Letters*, Vol. 4, No. 21, pp. 2507-2510, 1994, incorporated herein by reference, discloses exemplary pipecolic acid derivatives represented by Formulas VII-IX and Tables V-VII.

FORMULA VII

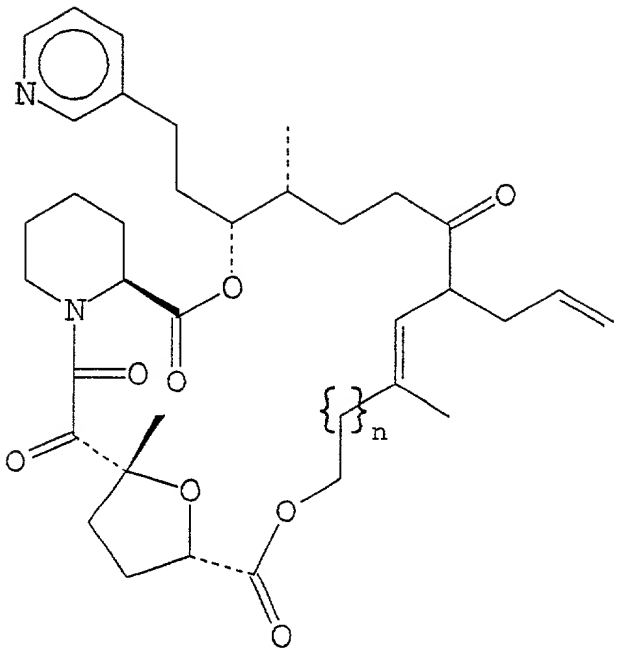


VII

TABLE V

Compound	Structure
22	y = 1
23	y = 2
24	y = 3

FORMULA VIII

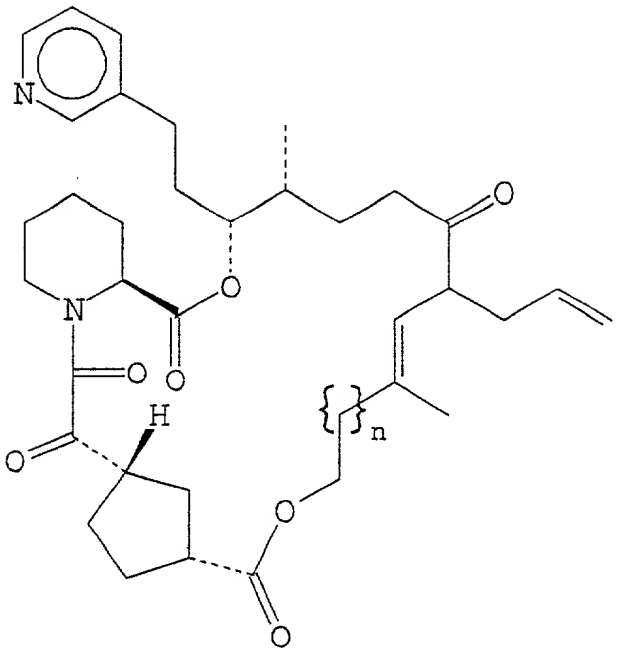


VIII

TABLE VI

Compound	Structure
25	n = 1
26	n = 2
27	n = 3

FORMULA IX



IX

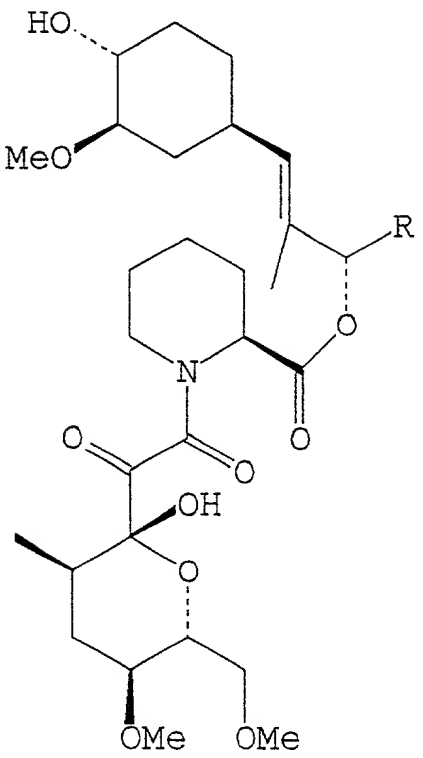
TABLE VII

Compound	Structure
28	n = 1
29	n = 2
30	n = 3

COMPOUND 31

Teague et al., *Bioorganic & Medicinal Chemistry Letters*, Vol. 3, No. 10, pp. 1947-1950, 1993, incorporated herein by reference, discloses an exemplary pipecolic acid derivative represented by Formula X.

FORMULA X

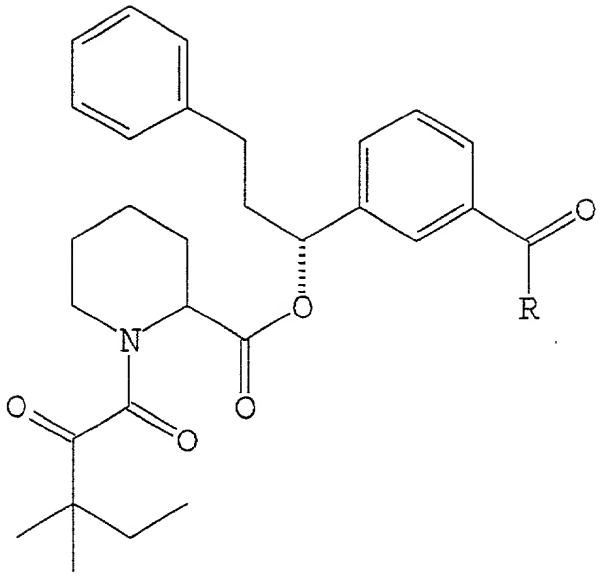


X

COMPOUNDS 32-34

Yamashita et al., *Bioorganic & Medicinal Chemistry Letters*, Vol. 4., No. 2, pp. 325-328, 1994, incorporated herein by reference, discloses exemplary pipecolic acid derivatives represented by Formula XI and Table VIII.

FORMULA XI

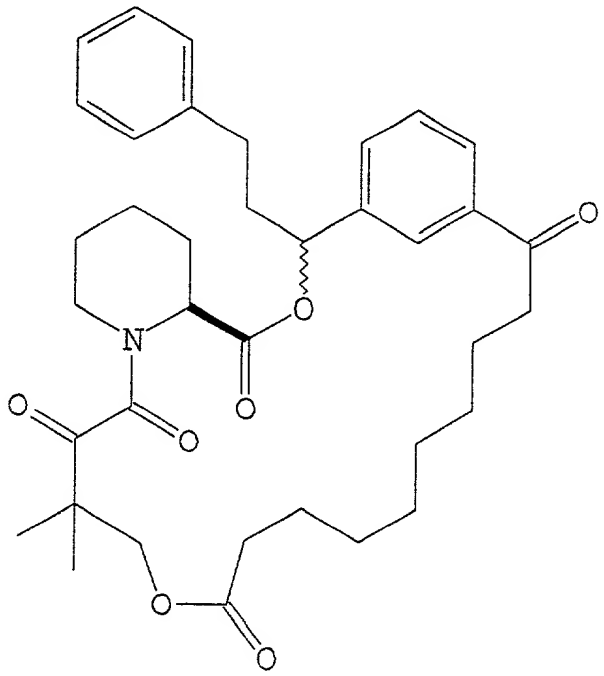


XI

TABLE VIII

Compound	Structure
32	R = phenyl
33	R = N(allyl)$_2$

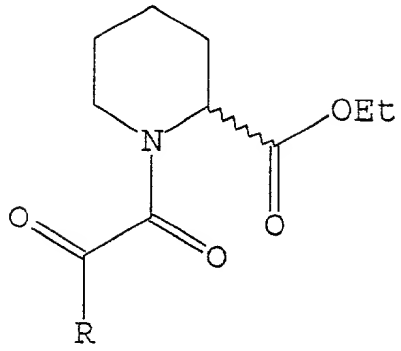
TABLE VIII (continued)

Compound	Structure
34	

COMPOUND 35-55

Holt et al., *Bioorganic & Medicinal Chemistry Letters*, Vol. 4, No. 2, pp. 315-320, 1994, incorporated herein by reference, discloses exemplary pipecolic acid derivatives represented by Formula XII and Tables IX-XI.

FORMULA XII



XII

TABLE IX

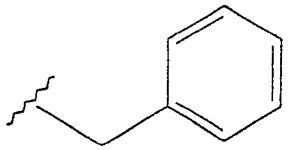
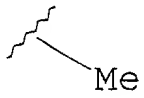
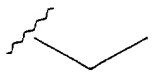
Compound	Structure
35	R = 
36	R = 
37	R = 

TABLE IX (continued)

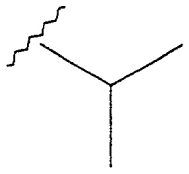
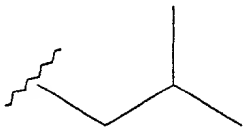
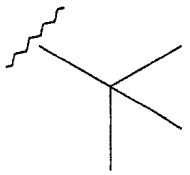
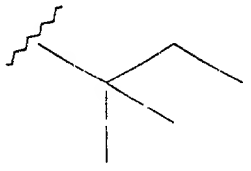
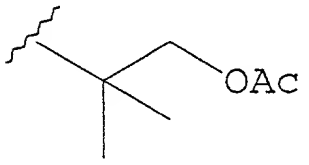
Compound	Structure
38	R = 
39	R = 
40	R = 
41	R = 
42	R = 

TABLE IX (continued)

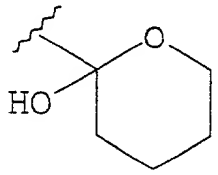
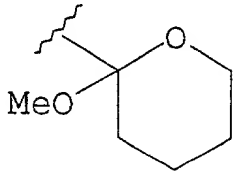
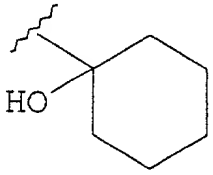
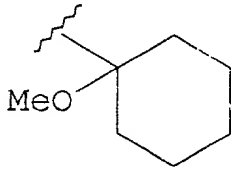
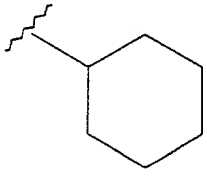
Compound	Structure
43	R = 
44	R = 
45	R = 
46	R = 
47	R = 

TABLE IX (continued)

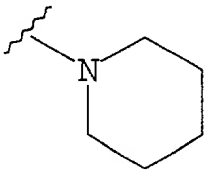
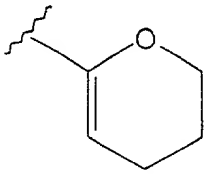
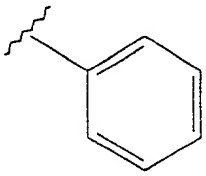
Compound	Structure
48	R = 
49	R = 
50	R = 

TABLE X

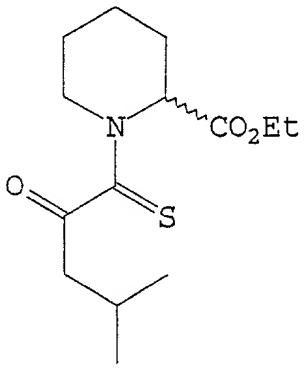
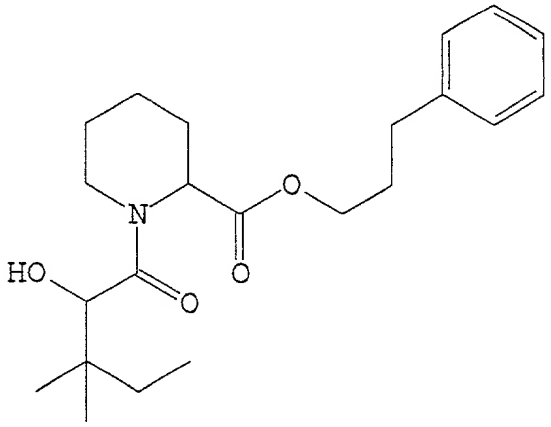
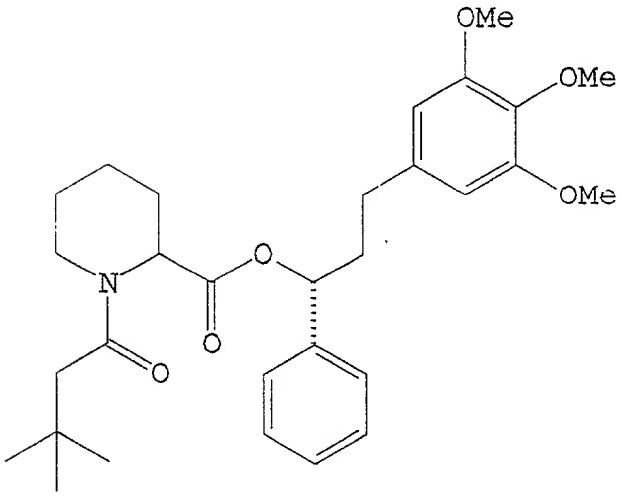
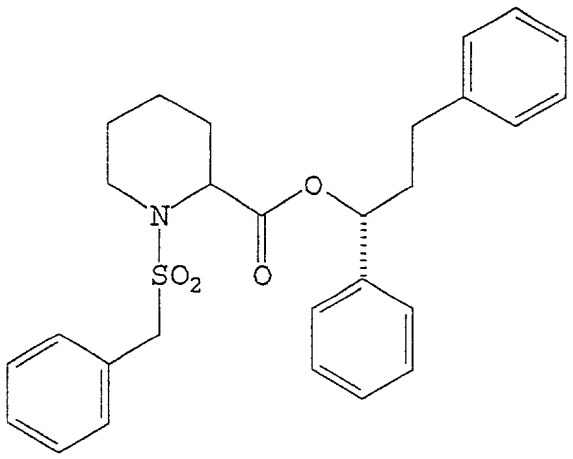
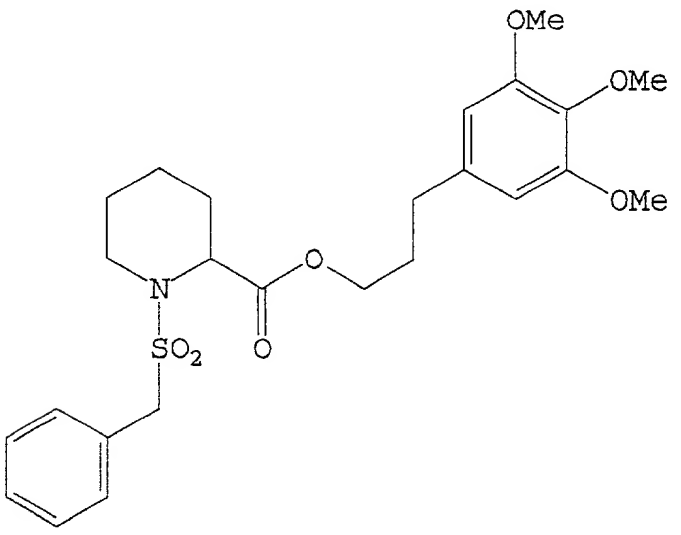
Compound	Structure
51	
52	
53	

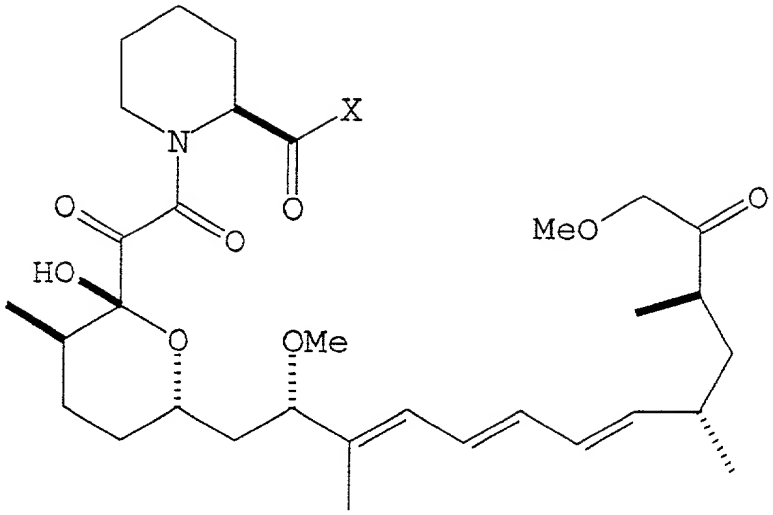
TABLE XI

Compound	Structure
54	
55	

COMPOUNDS 56-68

Holt et al., *Bioorganic & Medicinal Chemistry Letters*, Vol. 3, No. 10, pp. 1977-1980, 1993, incorporated herein by reference, discloses exemplary pipecolic acid derivatives represented by Formulas XIII and XIV and Tables XII-XIV.

FORMULA XIII

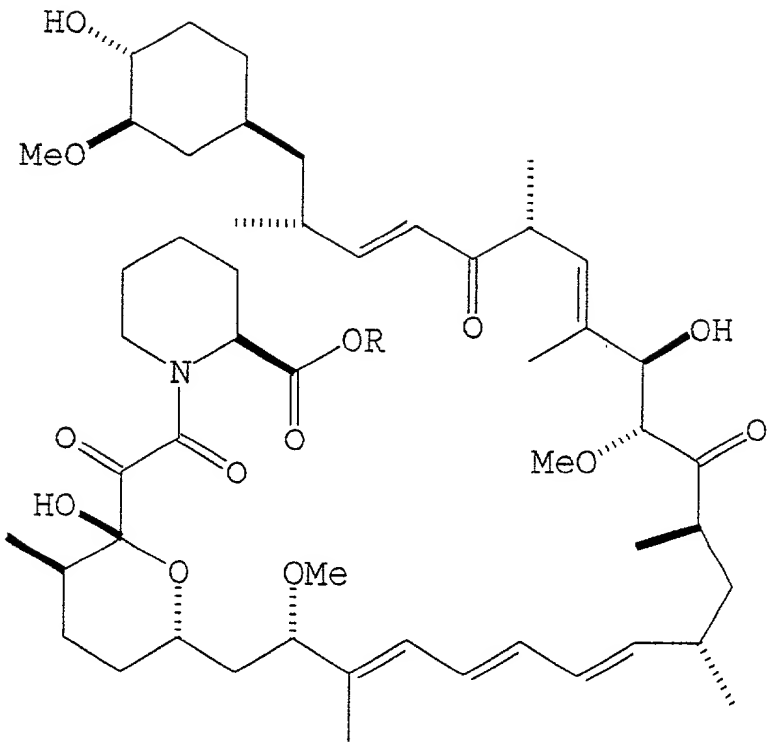


XIII

TABLE XII

Compound	Structure
56	X = OH
57	X = OMe
58	X = Oi Pr
59	X = OBn
60	X = OCH MePh
61	X = $OCH_2CHCHPh$
62	X = $OCH_2CH_2CH_2$(3,4-OMe_2)Ph
63	X = NHBn
64	X = $NHCH_2CH_2CH_2Ph$

FORMULA XIV

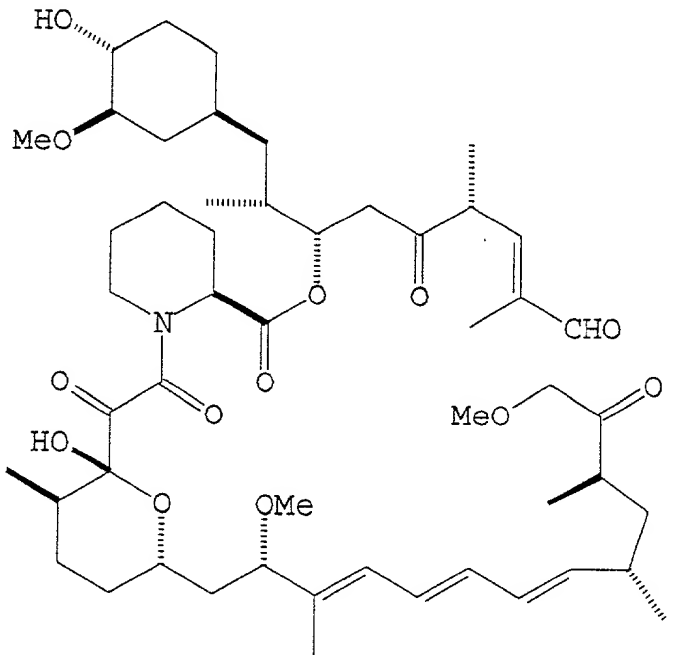
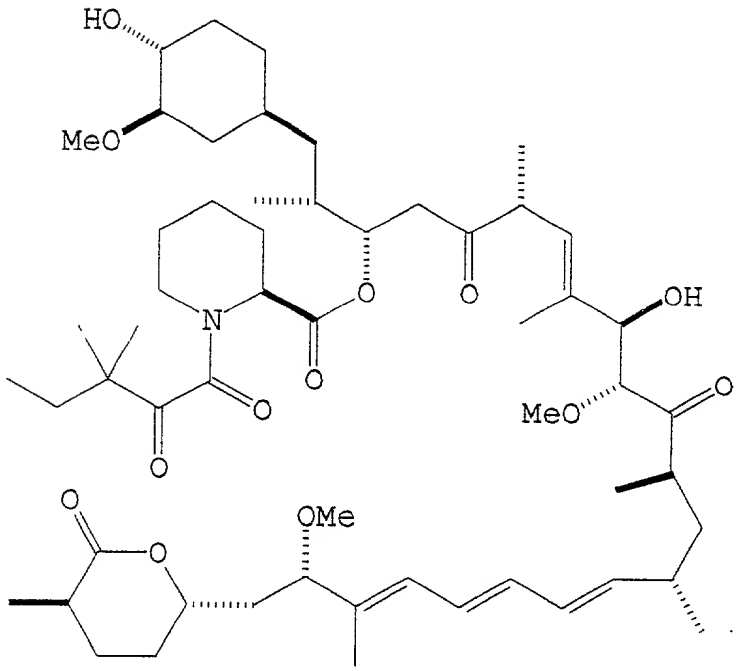


XIV

TABLE XIII

Compound	Structure
65	R = Me
66	R = Bn

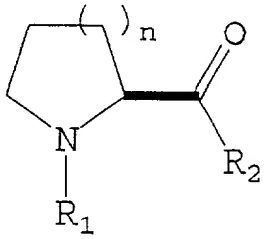
TABLE XIV

Compound	Structure
67	
68	

COMPOUNDS 69-83

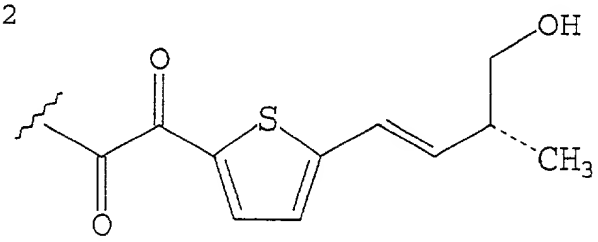
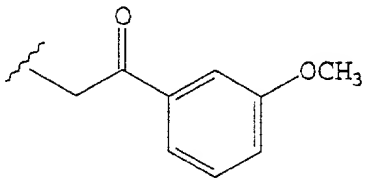
Hauske et al., *J. Med. Chem.*, Vol. 35, pp. 4284-4296, 1992, incorporated herein by reference, discloses exemplary pipecolic acid derivatives represented by Formulas XV-XVIII and Tables XV-XVIII.

FORMULA XV

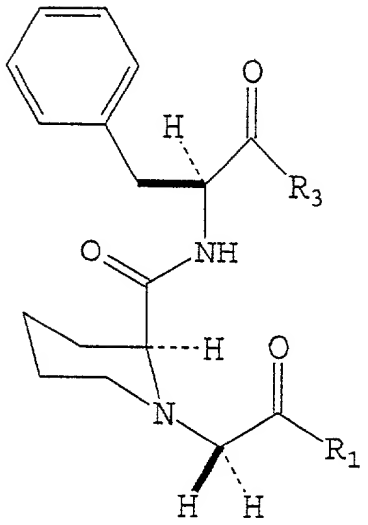


XV

TABLE XV

Compound	Structure
69	n = 2 R_1 =  R_2 = Phe-o-*tert*-butyl
70	n = 2 R_1 =  R_2 = Phe-o-*tert*-butyl

FORMULA XVI

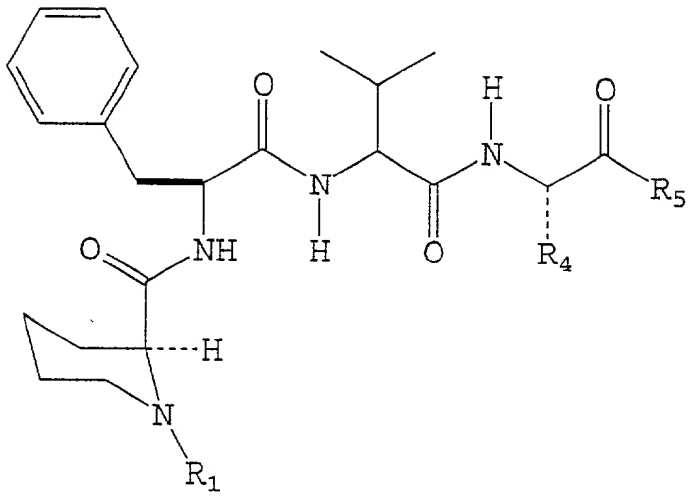


XVI

TABLE XVI

Compound	Structure
71	R_1 = *m*-OCH_3Ph R_3 = Val-O-*tert*-butyl
72	R_1 = *m*-OCH_3Ph R_3 = Leu-O-*tert*-butyl
73	R_1 = *m*-OCH_3Ph R_3 = Ileu-O-*tert*-butyl
74	R_1 = *m*-OCH_3Ph R_3 = hexahydro-Phe-O-*tert*-butyl
75	R_1 = *m*-OCH_3Ph R_3 = allylalanine-O-*tert*-butyl
76	R_1 = B-naphthyl R_3 = Val-O-*tert*-butyl

FORMULA XVII

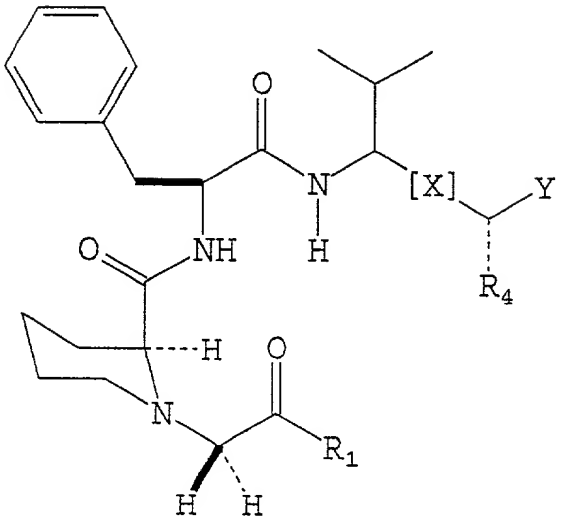


XVII

TABLE XVII

Compound	Structure
77	R_1 = $CH_2(CO)$-*m*-OCH_3Ph R_4 = CH_2Ph R_5 = OCH_3
78	R_1 = $CH_2(CO)$-*ß*-naphthyl R_4 = CH_2Ph R_5 = OCH_3

FORMULA XVIII



XVIII

TABLE XVIII

Compound	Structure
79	R_1 = *m*-OCH_3Ph X = *trans*-CH=CH R_4 = H Y = OC(O)Ph
80	R_1 = *m*-OCH_3Ph X = *trans*-CH=CH R_4 = H Y = $OC(O)CF_3$

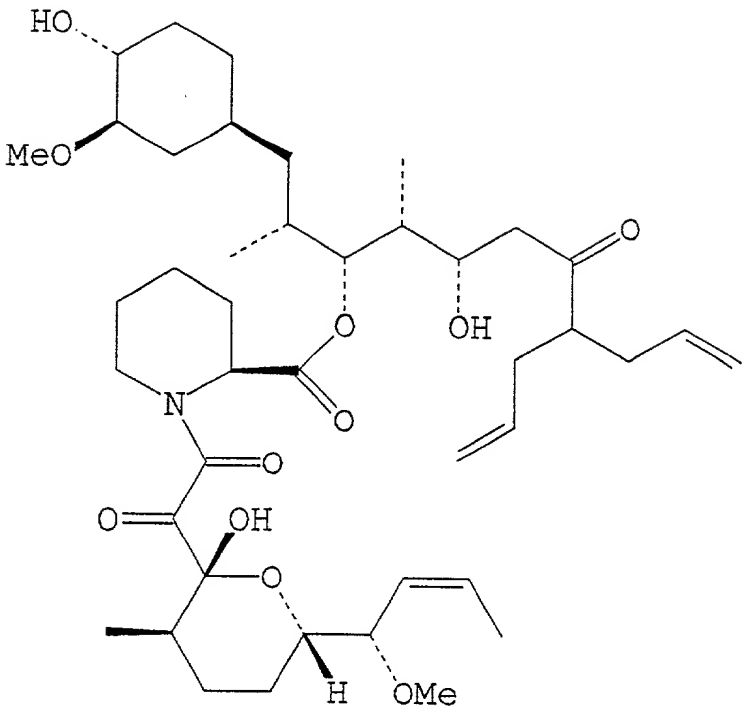
TABLE XVIII (continued)

Compound	Structure
81	R_1 = *m*-OCH_3Ph X = *trans*-CH=CHI R_4 = - Y = -
82	R_1 = *m*-OCH_3Ph X = *trans*-CH=CH R_4 = H Y = $OCH_2CH=CH_2$
83	R_1 = *m*-OCH_3Ph X = C=O R_4 = H Y = Ph

COMPOUND 84

Teague et al., *Bioorganic & Med. Chem. Letters*, Vol. 4, No. 13, pp. 1581-1584, 1994, incorporated herein by reference, discloses an exemplary pipecolic acid derivative represented by Formula XIX.

FORMULA XIX



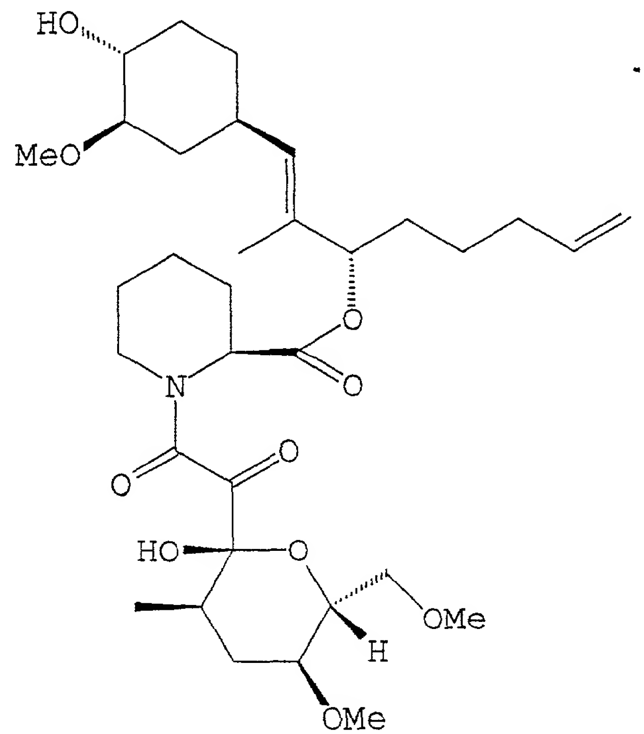
XIX

SLB506

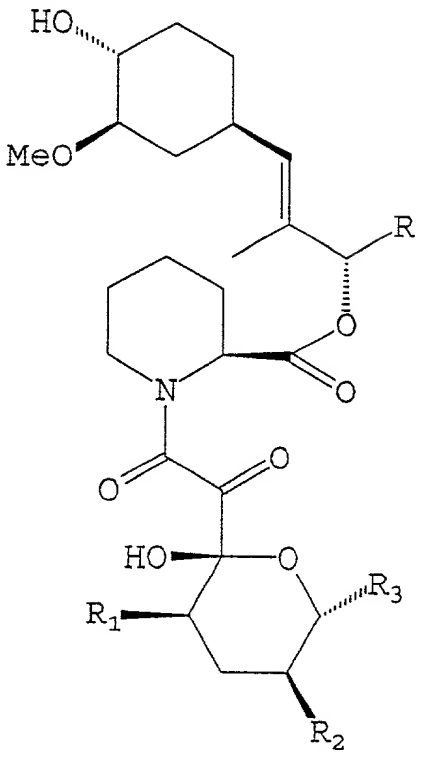
COMPOUNDS 85-88

Stocks et al., *Bioorganic & Med. Chem. Letters*, Vol. 4, No. 12, pp. 1457-1460, 1994, incorporated herein by reference, discloses exemplary pipecolic acid derivatives represented by Formula XX and Tables XIX and XX.

TABLE XIX

Compound	Structure
85	

FORMULA XX



XX

TABLE XX

Compound	Structure
86	R_1 = H R_2 = OMe R_3 = CH_2OMe
87	R_1 = H R_2 = H R_3 = H

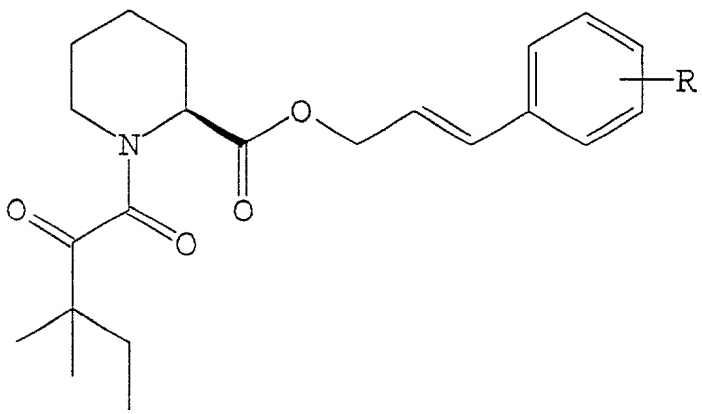
TABLE XX (continued)

Compound	Structure
88	R_1 = Me R_2 = H R_3 = H

COMPOUNDS 89-110

Additional exemplary pipecolic acid derivatives are represented by Formulas XXI-XXV and Tables XXI-XXV.

FORMULA XXI



XXI

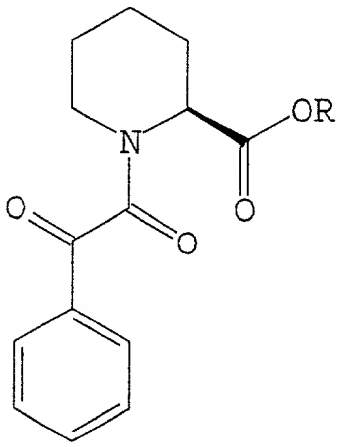
TABLE XXI

Compound	Structure
89	R = 3,4-dichloro
90	R = 3,4,5-trimethoxy

TABLE XXI (continued)

Compound	Structure
91	R = H
92	R = 3-(2,5-Dimethoxy)phenylpropyl
93	R = 3-(3,4-Methylenedioxy)phenyl-propyl

FORMULA XXII

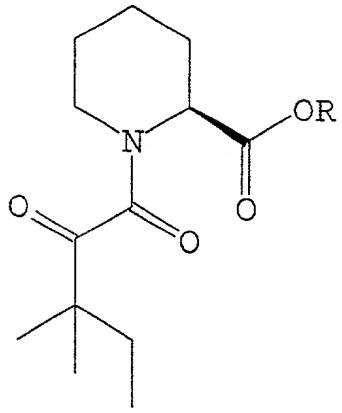


XXII

TABLE XXII

Compound	Structure
94	R = 4-(*p*-Methoxy)butyl
95	R = 3-Phenylpropyl
96	R = 3-(3-Pyridyl)propyl

FORMULA XXIII

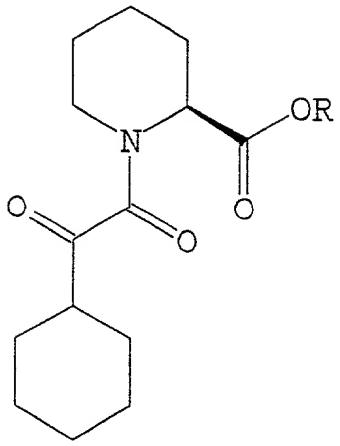


XXIII

TABLE XXIII

Compound	Structure
97	R = 3-(3-Pyridyl)propyl
98	R = 1,7-Diphenyl-4-heptyl
99	R = 4-(4-Methoxy)butyl
100	R = 1-Phenyl-6-(4-methoxyphenyl)-4-hexyl
101	R = 3-(2,5-Dimethoxy)phenylpropyl
102	R = 3-(3,4-Methylenedioxy)phenylpropyl
103	R = 1,5-Diphenylpentyl

FORMULA XXIV

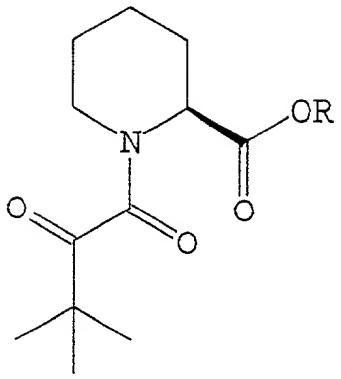


XXIV

TABLE XXIV

Compound	Structure
104	R = 4-(4-Methoxy)butyl
105	R = 3-Cyclohexylpropyl
106	R = 3-Phenylpropyl

FORMULA XXV



XXV

TABLE XXV

Compound	Structure
107	R = 3-Cyclohexylpropyl
108	R = 3-Phenylpropyl
109	R = 4-(4-Methoxy)butyl
110	R = 1,7-Diphenyl-4-heptyl

The names of some of the compounds identified above are provided below in Table XXVI.

TABLE XXVI

Compound	Name of Species
6	4-(4-methoxyphenyl)butyl (2*S*)-1-[2-(3,4,5-trimethoxyphenyl)acetyl]hexahydro-2-pyridinecarboxylate
7	4-(4-methoxyphenyl)butyl (2*S*)-1-[2-(3,4,5-trimethoxyphenyl)acryloyl]hexahydro-2-pyridinecarboxylate
8	4-(4-methoxyphenyl)butyl (2*S*)-1-[2-(3,4,5-trimethoxyphenyl)propanoyl]hexahydro-2-pyridinecarboxylate
9	4-(4-methoxyphenyl)butyl (2*S*)-1-[2-oxo-2-(3,4,5-trimethoxyphenyl)acetyl]hexahydro-2-pyridinecarboxylate
11	3-cyclohexylpropyl (2*S*)-1-(3,3-dimethyl-2-oxopentanoyl)hexahydro-2-pyridinecarboxylate
12	3-phenylpropyl (2*S*)-1-(3,3-dimethyl-2-oxopentanoyl)hexahydro-2-pyridinecarboxylate
13	3-(3,4,5-trimethoxyphenyl)propyl (2*S*)-1-(3,3-dimethyl-2-oxopentanoyl)hexahydro-2-pyridine-carboxylate

TABLE XXVI (continued)

Compound	Name of Species
14	(1*R*)-2,2-dimethyl-1-phenethyl-3-butenyl (2*S*)-1-(3,3-dimethyl-2-oxopentanoyl)hexahydro-2-pyridinecarboxylate
15	(1*R*)-1,3-diphenylpropyl (2*S*)-1-(3,3-dimethyl-2-oxopentanoyl)hexahydro-2-pyridinecarboxylate
16	(1*R*)-1-cyclohexyl-3-phenylpropyl (2*S*)-1-(3,3-dimethyl-2-oxopentanoyl)hexahydro-2-pyridine-carboxylate
17	(1*S*)-1,3-diphenylpropyl (2*S*)-1-(3,3-dimethyl-2-oxopentanoyl)hexahydro-2-pyridinecarboxylate
18	(1*S*)-1-cyclohexyl-3-phenylpropyl (2*S*)-1-(3,3-dimethyl-2-oxopentanoyl)hexanydro-2-pyridine-carboxylate
19	(22a*S*)-15,15-dimethylperhydropyrido[2,1-c][1,9,4]dioxazacyclononadecine-1,12,16,17-tetraone

TABLE XXVI (continued)

Compound	Name of Species
20	(24a*S*)-17,17-dimethylperhydropyrido[2,1-c][1,9,4]dioxazacyclohenicosine-1,14,18,19-tetraone
35	ethyl 1-(2-oxo-3-phenylpropanoyl)-2-piperidinecarboxylate
36	ethyl 1-pyruvoyl-2-piperidinecarboxylate
37	ethyl 1-(2-oxobutanoyl)-2-piperidine-carboxylate
38	ethyl 1-(3-methyl-2-oxobutanoyl)-2-piperidine-carboxylate
39	ethyl 1-(4-methyl-2-oxopentanoyl)-2-piperidinecarboxylate
40	ethyl 1-(3,3-dimethyl-2-oxobutanoyl)-2-piperidinecarboxylate
41	ethyl 1-(3,3-dimethyl-2-oxopentanoyl)-2-piperidinecarboxylate

TABLE XXVI (continued)

Compound	Name of Species
42	4-[2-(ethyloxycarbonyl)piperidino]-2,2-dimethyl-3,4-dioxobutyl acetate
43	ethyl 1-[2-(2-hydroxytetrahydro-2*H*-2-pyranyl)-2-oxoacetyl]-2-piperidinecarboxylate
44	ethyl 1-[2-(2-methoxytetrahydro-2*H*-2-pyranyl)-2-oxoacetyl]-2-piperidinecarboxylate
45	ethyl 1-[2-(1-hydroxycyclohexyl)-2-oxoacetyl]-2-piperidinecarboxylate
46	ethyl 1-[2-(1-methoxycyclohexyl)-2-oxoacetyl]-2-piperidinecarboxylate
47	ethyl 1-(2-cyclohexyl-2-oxoacetyl)-2-piperidinecarboxylate
48	ethyl 1-(2-oxo-2-piperidinoacetyl)-2-piperidinecarboxylate
49	ethyl 1-[2-(3,4-dihydro-2*H*-6-pyranyl)-2-oxoacetyl)-2-piperidinecarboxylate

TABLE XXVI (continued)

Compound	Name of Species
50	ethyl 1-(2-oxo-2-phenylacetyl)-2-piperidinecarboxylate
51	ethyl 1-(4-methyl-2-oxo-1-thioxopentyl)-2-piperidinecarboxylate
52	3-phenylpropyl 1-(2-hydroxy-3,3-dimethylpentanoyl)-2-piperidinecarboxylate
53	(1*R*)-1-phenyl-3-(3,4,5-trimethoxyphenyl)propyl 1-(3,3-dimethylbutanoyl)-2-piperidine-carboxylate
54	(1*R*)-1,3-diphenylpropyl 1-(benzylsulfonyl)-2-piperidinecarboxylate
55	3-(3,4,5-trimethoxyphenyl)propyl 1-(benzylsulfonyl)-2-piperidinecarboxylate
56	1-(2-[(2*R*,3*R*,6*S*)-6-[(2*S*,3*E*,5*E*,7*E*,9*S*,11*R*)-2,13-dimethoxy-3,9,11-trimethyl-12-oxo-3,5,7-tridecatrienyl]-2-hydroxy-3-methyltetrahydro-2*H*-2-pyranyl)-2-oxoacetyl)-2-piperidine-carboxylic acid

TABLE XXVI (continued)

Compound	Name of Species
57	methyl 1-(2-[(2*R*,3*R*,6*S*)-6-[(2*S*,3*E*,5*E*,7*E*,9*S*,11*R*)-2,13-dimethoxy-3,9,11-trimethyl-12-oxo-3,5,7-tridecatrienyl]-2-hydroxy-3-methyl-tetrahydro-2*H*-2-pyranyl)-2-oxoacetyl)-2-piperidinecarboxylate
58	isopropyl 1-(2-[(2*R*,3*R*,6*S*)-6-[(2*S*,3*E*,5*E*,7*E*,9*S*,11*R*)-2,13-dimethoxy-3,9,11-trimethyl-12-oxo-3,5,7-tridecatrienyl]-2-hydroxy-3-methyl-tetrahydro-2*H*-2-pyranyl)-2-oxoacetyl)-2-piperidinecarboxylate
59	benzyl 1-(2-[(2*R*,3*R*,6*S*)-6-[(2*S*,3*E*,5*E*,7*E*,9*S*,11*R*)-2,13-dimethoxy-3,9,11-trimethyl-12-oxo-3,5,7-tridecatrienyl]-2-hydroxy-3-methyl-tetrahydro-2*H*-2-pyranyl)-2-oxoacetyl)-2-piperidinecarboxylate
60	1-phenylethyl 1-(2-[(2*R*,3*R*,6*S*)-6-[(2*S*,3*E*,5*E*,7*E*,9*S*,11*R*)-2,13-dimethoxy-3,9,11-trimethyl-12-oxo-3,5,7-tridecatrienyl]-2-hydroxy-3-methyl-tetrahydro-2*H*-2-pyranyl)-2-oxoacetyl)-2-piperidinecarboxylate

TABLE XXVI (continued)

Compound	Name of Species
61	(Z)-3-phenyl-2-propenyl 1-(2-[(2*R*,3*R*,6*S*)-6-[(2*S*,3*E*,5*E*,7*E*,9*S*,11*R*)-2,13-dimethoxy-3,9,11-trimethyl-12-oxo-3,5,7-tridecatrienyl]-2-hydroxy-3-methyltetrahydro-2*H*-2-pyranyl)-2-oxoacetyl)-2-piperidinecarboxylate
62	3-(3,4-dimethoxyphenyl)propyl 1-(2-[(2*R*,3*R*,6*S*)-6-[(2*S*,3*E*,5*E*,7*E*,9*S*,11*R*)-2,13-dimethoxy-3,9,11-trimethyl-12-oxo-3,5,7-tridecatrienyl]-2-hydroxy-3-methyltetrahydro-2*H*-2-pyranyl)-2-oxoacetyl)-2-piperidine-carboxylate
63	*N*2-benzyl-1-(2-[(2*R*,3*R*,6*S*)-6-[(2*S*,3*E*,5*E*,7*E*,9*S*, 11*R*)-2,13-dimethoxy-3,9,11-trimethyl-12-oxo-3,5,7-tridecatrienyl]-2-hydroxy-3-methyl-tetrahydro-2*H*-2-pyranyl)-2-oxoacetyl)-2-piperidinecarboxylate
64	*N*2-(3-phenylpropyl)-1-(2-[(2*R*,3*R*,6*S*)-6-[(2*S*,3*E*,5*E*,7*E*,9*S*,11*R*)-2,13-dimethoxy-3,9,11-trimethyl-12-oxo-3,5,7-tridecatrienyl]-2-hydroxy-3-methyltetrahydro-2*H*-2-pyranyl)-2-oxoacetyl)-2-piperidinecarboxylate.

TABLE XXVI (continued)

Compound	Name of Species
89	(*E*)-3-(3,4-dichlorophenyl)-2-propenyl 1-(3,3-dimethyl-2-oxopentanoyl)-2-piperidinecarboxylate
90	(*E*)-3-(3,4,5-trimethoxyphenyl)-2-propenyl 1-(3,3-dimethyl-2-oxopentanoyl)-2-piperidinecarboxylate
91	(*E*)-3-phenyl-2-propenyl 1-(3,3-dimethyl-2-oxo-pentanoyl)-2-piperidinecarboxylate
92	(*E*)-3-((3-(2,5-dimethoxy)-phenylpropyl)-phenyl)-2-propenyl 1-(3,3-dimethyl-2-oxopentanoyl)-2-piperidinecarboxylate
93	(*E*)-3-(1,3-benzodioxol-5-yl)-2-propenyl 1-(3,3-dimethyl-2-oxopentanoyl)-2-piperidinecarboxylate
94	4-(4-methoxyphenyl)butyl 1-(2-oxo-2-phenylacetyl)-2-piperidinecarboxylate
95	3-phenylpropyl 1-(2-oxo-2-phenylacetyl)-2-piperidinecarboxylate

TABLE XXVI (continued)

Compound	Name of Species
96	3-(3-pyridyl)propyl 1-(2-oxo-2-phenylacetyl)-2-piperidinecarboxylate
97	3-(3-pyridyl)propyl 1-(3,3-dimethyl-2-oxopentanoyl)-2-piperidinecarboxylate
98	4-phenyl-1-(3-phenylpropyl)butyl 1-(3,3-dimethyl-2-oxopentanoyl)-2-piperidine-carboxylate
99	4-(4-methoxyphenyl)butyl 1-(3,3-dimethyl-2-oxopentanoyl)-2-piperidinecarboxylate
100	1-(4-methoxyphenethyl)-4-phenylbutyl 1-(3,3-dimethyl-2-oxopentanoyl)-2-piperidine-carboxylate
101	3-(2,5-dimethoxyphenyl)propyl 1-(3,3-dimethyl-2-oxopentanoyl)-2-piperidinecarboxylate
102	3-(1,3-benzodioxol-5-yl)propyl 1-(3,3-dimethyl-2-oxopentanoyl)-2-piperidine-carboxylate

TABLE XXVI (continued)

Compound	Name of Species
103	1-phenethyl-3-phenylpropyl 1-(3,3-dimethyl-2-oxopentanoyl)-2-piperidinecarboxylate
104	4-(4-methoxyphenyl)butyl 1-(2-cyclohexyl-2-oxoacetyl)-2-piperidinecarboxylate
105	3-cyclohexylpropyl 1-(2-cyclohexyl-2-oxoacetyl)-2-piperidinecarboxylate
106	3-phenylpropyl 1-(2-cyclohexyl-2-oxoacetyl)-2-piperidinecarboxylate
107	3-cyclohexylpropyl 1-(3,3-dimethyl-2-oxobutanoyl)-2-piperidinecarboxylate
108	3-phenylpropyl 1-(3,3-dimethyl-2-oxobutanoyl)-2-piperidinecarboxylate
109	4-(4-methoxyphenyl)butyl 1-(3,3-dimethyl-2-oxobutanoyl)-2-piperidinecarboxylate
110	4-phenyl-1-(3-phenylpropyl)butyl 1-(3,3-dimethyl-2-oxobutanoyl)-2-piperidine-carboxylate

All the compounds of Formulas I-XXV possess asymmetric centers and thus can be produced as mixtures of stereoisomers or as individual R- and S-stereoisomers. The individual stereoisomers may be obtained by using an optically active starting material, by resolving a racemic or non-racemic mixture of an intermediate at some appropriate stage of the synthesis, or by resolving the compounds of Formulas I-XXV. It is understood that the compounds of Formulas I-XXV encompass individual stereoisomers as well as mixtures (racemic and non-racemic) of stereoisomers. Preferably, S-stereoisomers are used in the pharmeceutical compositions and methods of the present invention.

Affinity for FKBP12

The compounds used in the inventive methods and pharmaceutical compositions have an affinity for the FK506 binding protein, particularly FKBP12. The inhibition of the prolyl peptidyl *cis-trans* isomerase activity of FKBP may be measured as an indicator of this affinity.

K_i Test Procedure

Inhibition of the peptidyl-prolyl isomerase (rotamase) activity of the compounds used in the inventive methods and pharmaceutical compositions can be evaluated by known methods described in the

literature (Harding et al., *Nature*, 1989, 341:758-760; Holt et al. *J. Am. Chem. Soc.*, 115:9923-9938). These values are obtained as apparent K_i's and are presented for representative compounds in TABLE XXVII.

The *cis-trans* isomerization of an alanine-proline bond in a model substrate, N-succinyl-Ala-Ala-Pro-Phe-*p*-nitroanilide, is monitored spectrophotometrically in a chymotrypsin-coupled assay, which releases *para*-nitroanilide from the *trans* form of the substrate. The inhibition of this reaction caused by the addition of different concentrations of inhibitor is determined, and the data is analyzed as a change in first-order rate constant as a function of inhibitor concentration to yield the apparent K_i values.

In a plastic cuvette are added 950 mL of ice cold assay buffer (25 mM HEPES, pH 7.8, 100 mM NaCl), 10 mL of FKBP (2.5 mM in 10 mM Tris-Cl pH 7.5, 100 mM NaCl, 1 mM dithiothreitol), 25 mL of chymotrypsin (50 mg/ml in 1 mM HCl) and 10 mL of test compound at various concentrations in dimethyl sulfoxide. The reaction is initiated by the addition of 5 mL of substrate (succinyl-Ala-Phe-Pro-Phe-*para*-nitroanilide, 5 mg/mL in 2.35 mM LiCl in trifluoroethanol).

The absorbance at 390 nm versus time is monitored for 90 seconds using a spectrophotometer and the rate constants are determined from the absorbance versus time data files.

TABLE XXVII

In Vitro Test Results - Formulas I-XXV

Compound	K_i (μM)
6	140
9	13
11	170
12	250
13	25
15	17
19	12
36	>10,000
41	1300
50	>10,000
89	1800
90	28
91	39
92	75
93	70
94	165
95	740
96	725
97	130
98	30
99	60
100	15
101	12
102	120

TABLE XXVII (continued)

In Vitro Test Results - Formulas I-XXV

Compound	K_i (μM)
103	20
104	103
105	760
106	210
107	32
108	2
109	24
110	5

Route of Administration

To effectively treat alopecia or promote hair growth, the compounds used in the inventive methods and pharmaceutical compositions must readily affect the targeted areas. For these purposes, the compounds are preferably administered topically to the skin.

For topical application to the skin, the compounds can be formulated into suitable ointments containing the compounds suspended or dissolved in, for example, mixtures with one or more of the following: mineral oil, liquid petrolatum, white petrolatum, propylene glycol, polyoxyethylene polyoxypropylene compound, emulsifying wax and water. Alternatively, the compounds can be formulated into suitable lotions or creams containing the active

compound suspended or dissolved in, for example, a mixture of one or more of the following: mineral oil, sorbitan monostearate, polysorbate 60, cetyl ester wax, cetearyl alcohol, 2-octyldodecanol, benzyl alcohol and water.

Other routes of administration known in the pharmaceutical art are also contemplated by this invention.

Dosage

Dosage levels on the order of about 0.1 mg to about 10,000 mg of the active ingredient compound are useful in the treatment of the above conditions, with preferred levels of about 0.1 mg to about 1,000 mg. The specific dose level for any particular patient will vary depending upon a variety of factors, including the activity of the specific compound employed; the age, body weight, general health, sex and diet of the patient; the time of administration; the rate of excretion; drug combination; the severity of the particular disease being treated; and the form of administration. Typically, *in vitro* dosage-effect results provide useful guidance on the proper doses for patient administration. Studies in animal models are also helpful. The considerations for determining the proper dose levels are well known in the art.

The compounds can be administered with other hair revitalizing agents. Specific dose levels for the

other hair revitalizing agents will depend upon the factors previously stated and the effectiveness of the drug combination.

EXAMPLES

The following examples are illustrative of the present invention and are not intended to be limitations thereon. Unless otherwise indicated, all percentages are based upon 100% by weight of the final composition.

Example 1

In Vivo Hair Generation Tests With C57 Black 6 Mice

Experiment A: C57 black 6 mice were used to demonstrate the hair revitalizing properties of pipecolic acid derivatives GPI 1116 and GPI 1102, as well as related pipecolic acid derivative neuroimmunophilin FKBP ligand GPI 1044. C57 black 6 mice, approximately 7 weeks old, had an area of about 2 inches by 2 inches on their hindquarters shaved to remove all existing hair. Care was taken not to nick or cause abrasion to the underlaying dermal layers. The animals were in anagen growth phase, as indicated by the pinkish color of the skin. Referring now to FIGS. 1, 2, and 3, four animals were treated by topical administration with 20% propylene glycol vehicle (FIG. 1), and seven animals per group were treated by topical administration with 10 μM GPI 1116

(FIG. 2), or 3 μM GPI 1102 (FIG. 3). The animals were treated with vehicle, GPI 1116, or GPI 1102 every 48 hours (3 applications total over the course of 5 days) and the hair growth was allowed to proceed for 6 weeks. Hair growth was quantitated by the percent of shaved area covered by new hair growth during this time period.

FIG. 1 shows that animals treated with vehicle exhibited only a small amount of hair growth in patches or tufts, with less than 3% of the shaved area covered with new growth. In contrast, FIGS. 2 and 3 show that animals treated with 10 μM GPI 1116 and 3 μM GPI 1102 exhibited dramatic hair growth, covering as much as 50% of the shaved area in some animals. FIG. 4 compares the hair growth score of unshaven animals with the hair growth scores of shaven animals treated with a vehicle, GPI 1116 (1 μM and 10 μM), GPI 1102 (1 μM and 3 μM), and related neuroimmunophilin FKBP ligand GPI 1044 (1 μM, 3 μM and 10 μM).

Experiment B: C57 Black 6 mice were used to demonstrate the hair revitalizing properties of neuroimmunophilin FKBP ligands, including GPI 1116. C57 Black 6 mice, 55 to 75 days old, had an area of about 2 inches by 2 inches on their hindquarters shaved to remove all existing hair. Care was taken not to nick or cause abrasion to the underlying dermal layers. The animals were in a anagen growth phase when shaved. Five animals per group were treated by

topical administration with a vehicle, FK506, or a neuroimmunophilin FKBP ligand (GPI 1116 or 1206) at a concentration of one micromole per milliliter to the shaved area. The animals were treated three times per week, and hair growth was evaluated 14 days after initiation of treatment. Hair growth was quantitated by the percent of shaved area covered by new hair growth, as scored by a blinded observer, on a scale of 0 (no growth) to five (complete hair regrowth in shaved area).

Figure 5 shows that after 14 days, the animals treated with vehicle exhibited the beginning of growth in small tufts. In contrast, animals treated with one of the neuroimmunophilin FKBP ligands exhibited dramatic hair growth.

Example 2

A lotion comprising the following composition may be prepared.

	(%)
95% Ethanol	80.0
a pipecolic acid derivative as defined above	10.0
α-Tocopherol acetate	0.01
Ethylene oxide (40 mole) adducts of hardened castor oil	0.5
purified water	9.0
perfume and dye	q.s.

Into 95% ethanol are added a pipecolic acid derivative, α-tocopherol acetate, ethylene oxide (40 mole) adducts of hardened castor oil, perfume and a dye. The resulting mixture is stirred and dissolved, and purified water is added to the mixture to obtain a transparent liquid lotion.

5 ml of the lotion may be applied once or twice per day to a site having marked baldness or alopecia.

Example 3

A lotion comprising the following composition shown may be prepared.

	(%)
95% Ethanol	80.0
a pipecolic acid derivative as defined above	0.005
Hinokitol	0.01
Ethylene oxide (40 mole) adducts of hardened castor oil	0.5
Purified water	19.0
Perfume and dye	q.s.

Into 95% ethanol are added a pipecolic acid derivative, hinokitol, ethylene oxide (40 mole) adducts of hardened castor oil, perfume, and a dye. The resulting mixture is stirred, and purified water is added to the mixture to obtain a transparent liquid lotion.

The lotion may be applied by spraying once to 4 times per day to a site having marked baldness or alopecia.

Example 4

An emulsion may be prepared from A phase and B phase having the following compositions.

(A phase)	(%)
Whale wax	0.5
Cetanol	2.0
Petrolatum	5.0
Squalane	10.0
Polyoxyethylene (10 mole) monostearate	2.0
Sorbitan monooleate	1.0
a pipecolic acid derivative as defined above	0.01
(B phase)	(%)
Glycerine	10.0
Purified water	69.0
Perfume, dye, and preservative	q.s.

The A phase and the B phase are respectively heated and melted and maintained at 80°c. Both phases are then mixed and cooled under stirring to normal temperature to obtain an emulsion.

The emulsion may be applied by spraying once to four times per day to a site having marked baldness or alopecia.

Example 5

A cream may be prepared from A phase and B phase having the following compositions.

(A Phase)	(%)
Fluid paraffin	5.0
Cetostearyl alcohol	5.5
Petrolatum	5.5
Glycerine monostearate	33.0
Polyoxyethylene (20 mole) 2-octyldodecyl ether	3.0
Propylparaben	0.3
(B Phase)	(%)
a pipecolic acid derivative as defined above	0.8
Glycerine	7.0
Dipropylene glycol	20.0
Polyethylene glycol 4000	5.0
Sodium Hexametaphosphate	0.005
Purified water	44.895

The A phase is heated and melted, and maintained at 70°c. The B phase is added into the A phase and the mixture is stirred to obtain an emulsion. The emulsion is then cooled to obtain a cream.

The cream may be applied once to 4 times per day to a site having marked baldness or alopecia.

Example 6

A liquid comprising the following composition may be prepared.

	(%)
Polyoxyethylene butyl ether	20.0
Ethanol	50.0
a pipecolic acid derivative as defined above	0.001
Propylene glycol	5.0
Polyoxyethylene hardened castor oil derivative (ethylene oxide 80 mole adducts)	0.4
Perfume	q.s.
Purified water	q.s.

Into ethanol are added polyoxypropylene butyl ether, propylene glycol, polyoxyethylene hardened castor oil, a pipecolic acid derivative, and perfume. The resulting mixture is stirred, and purified water is added to the mixture to obtain a liquid.

The liquid may be applied once to 4 times per day to a site having marked baldness or alopecia.

Example 7

A shampoo comprising the following composition may be prepared.

	(%)
Sodium laurylsulfate	5.0
Triethanolamine laurylsulfate	5.0
Betaine lauryldimethylaminoacetate	6.0
Ethylene glycol distearate	2.0
Polyethylene glycol	5.0
a pipecolic acid derivative as defined above	5.0
Ethanol	2.0
Perfume	0.3
Purified water	69.7

Into 69.7 of purified water are added 5.0 g of sodium laurylsulfate, 5.0 g of triethanolamine laurylsulfate, 6.0 g of betaine lauryldimethyl-aminoacetate. Then a mixture obtained by adding 5.0 g of a pipecolic acid derivative, 5.0 g of polyethylene glycol, and 2.0 g of ethylene glycol distearate to 2.0 g of ethanol, followed by stirring, and 0.3 g of perfume are successively added. The resulting mixture is heated and subsequently cooled to obtain a shampoo.

The shampoo may be used on the scalp once or twice per day.

Example 8

A patient is suffering from alopecia senilis. A pipecolic acid derivative as identified above, or a pharmaceutical composition comprising the same, may be administered to the patient. Increased hair growth is expected to occur following treatment.

Example 9

A patient is suffering from male pattern alopecia. A pipecolic acid derivative as identified above, or a pharmaceutical composition comprising the same, may be administered to the patient. Increased hair growth is expected to occur following treatment.

Example 10

A patient is suffering from alopecia areata. A pipecolic acid derivative as identified above, or a pharmaceutical composition comprising the same, may be administered to the patient. Increased hair growth is expected to occur following treatment.

Example 11

A patient is suffering from hair loss caused by skin lesions. A pipecolic acid derivative as identified above, or a pharmaceutical composition comprising the same, may be administered to the patient. Increased hair growth is expected to occur following treatment.

Example 12

A patient is suffering from hair loss caused by tumors. A pipecolic acid derivative as identified above, or a pharmaceutical composition comprising the same, may be administered to the patient. Increased hair growth is expected to occur following treatment.

Example 13

A patient is suffering from hair loss caused by a systematic disorder, such as a nutritional disorder or an internal secretion disorder. A pipecolic acid derivative as identified above, or a pharmaceutical composition comprising the same, may be administered to the patient. Increased hair growth is expected to occur following treatment.

Example 14

A patient is suffering from hair loss caused by chemotherapy. A pipecolic acid derivative as identified above, or a pharmaceutical composition comprising the same, may be administered to the patient. Increased hair growth is expected to occur following treatment.

Example 15

A patient is suffering from hair loss caused by radiation. A pipecolic acid derivative as identified above, or a pharmaceutical composition comprising the

same, may be administered to the patient. Increased hair growth is expected to occur following treatment.

The invention being thus described, it will be obvious that the same may be varied in many ways. Such variations are not to be regarded as a departure from the spirit and scope of the invention and all such modifications are intended to be included within the scope of the following claims.